Field synopsis – Coronary Heart Disease (CHD)

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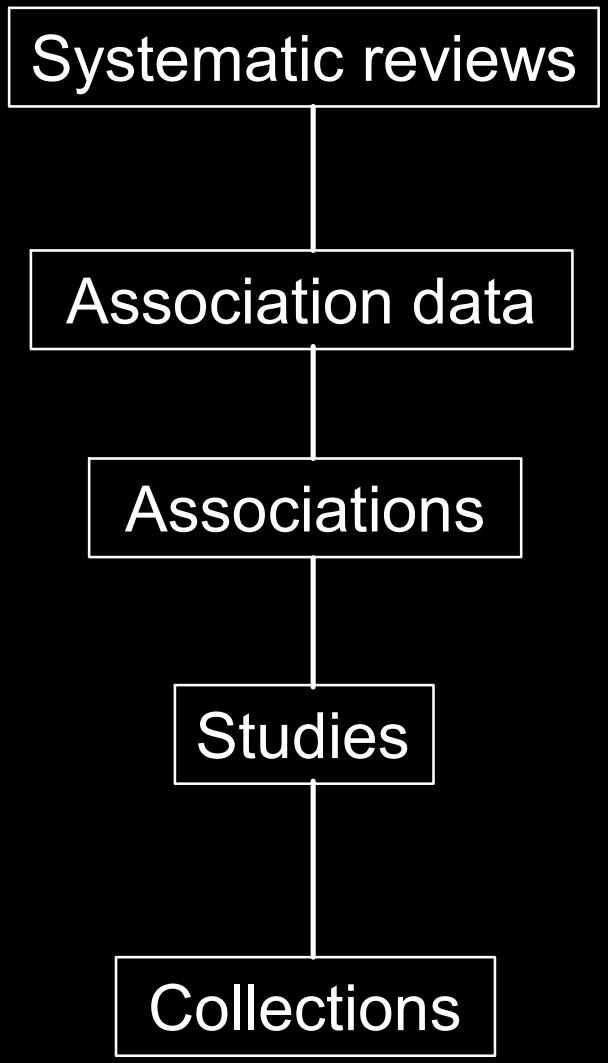
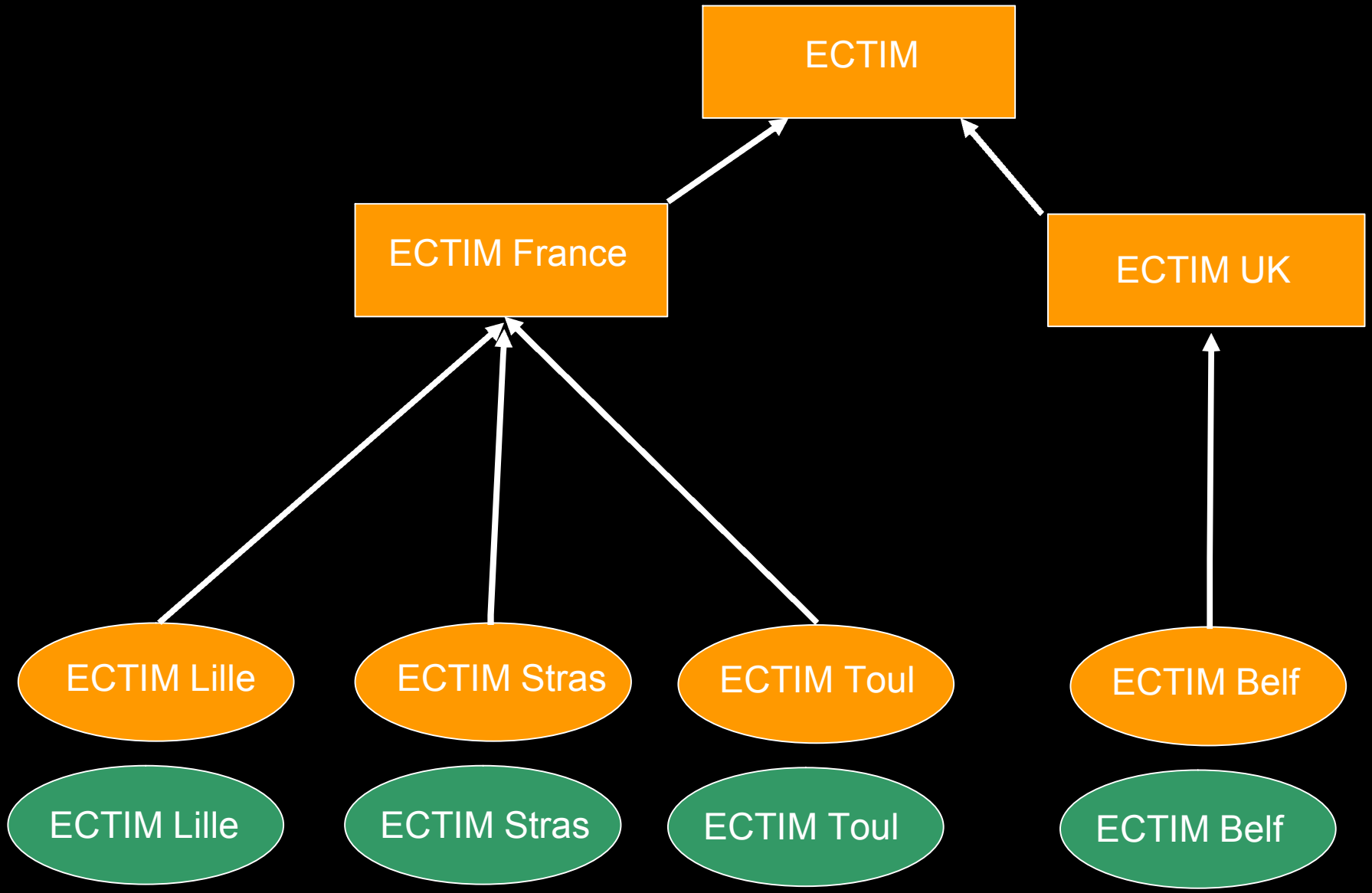
HuGENet

“Top-down” approach

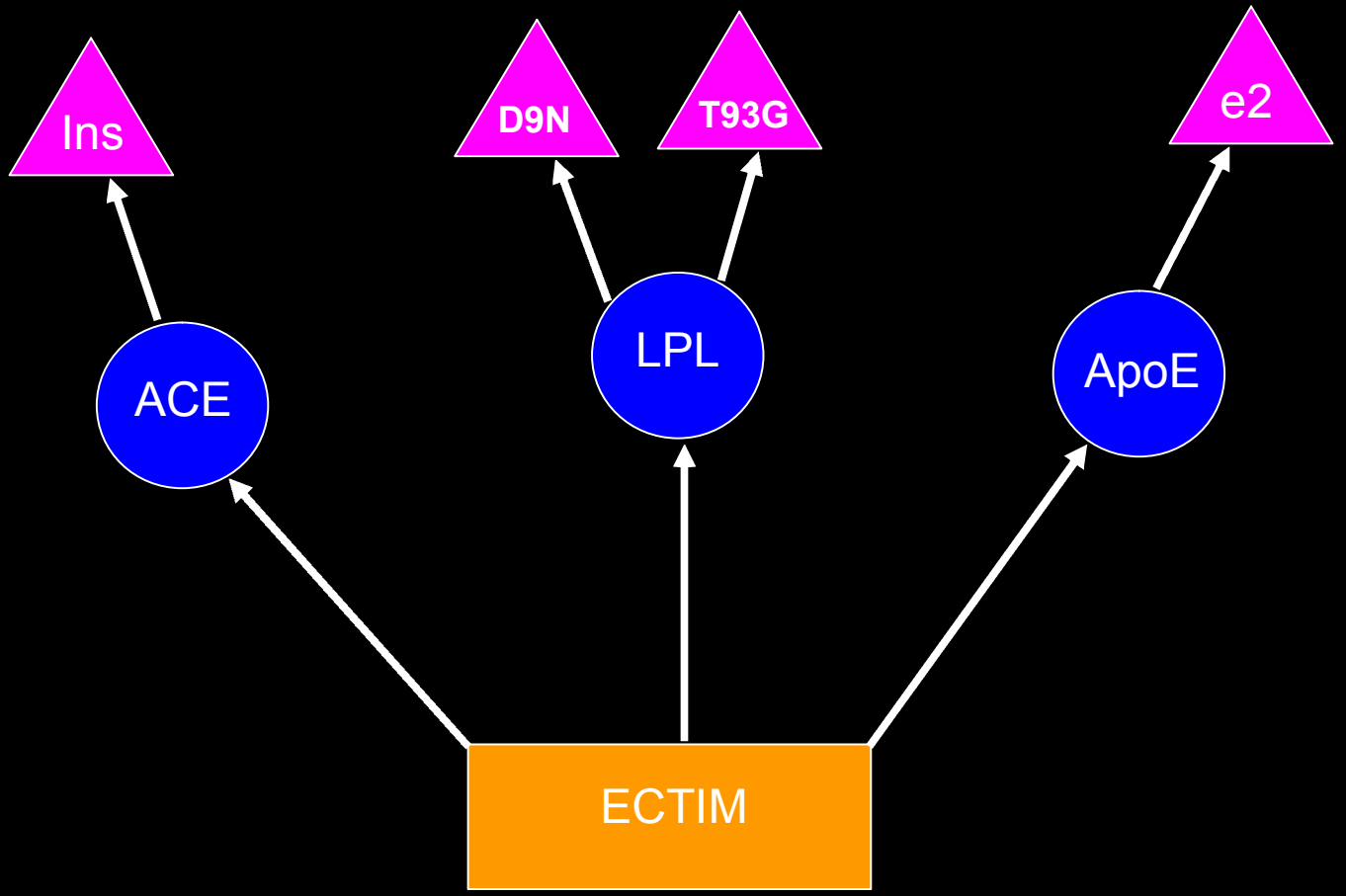


Database example - ECTIM



Database example - ECTIM

Systematic reviews



Issues

- Narrow, but very focused approach
- Time spent developing complex relational database to accommodate such multiplicity
- Web forms and parsing tools developed to facilitate input of data
- Identification of same studies (or study subsets) extremely time-consuming!
- Not helped by duplicate publication of data and inadequate reporting of details of study participants

Database contents

- Published reviews on 32 genes containing 45 variants
- 1078 associations tested (mean 24/review, range 2-121)
- >6000 rows of genotype data
- 529 distinct studies (max 14 associations/study)
- 746 collections (max 26 associations/collection)

- 713 published reports
- ~3000 people

Summary effect estimates

- Summary ORs estimated using relatively complex model to partially address reporting problems:

1. To ensure a consistent inheritance model:
   - Per-allele OR estimated even if dominant or recessive model reported (Salanti & Higgins, Stat Med 2008; 27(5): 764-77.)
2. To tackle dependence of findings on sample size:
   - Regression of lnOR on log sample size included in the model, with predicted value at sample size equivalent to largest study in the meta-analysis used as the summary result (Shang et al., Lancet 2005; 366:726-32.)
   - Implemented using Monte Carlo Markov chain methods (WinBUGS)

CHD - overall picture

Biological pathway	Gene	Variant	Assoc	Total
Lipids				
	apoE	e2/e3/e4	121	120577
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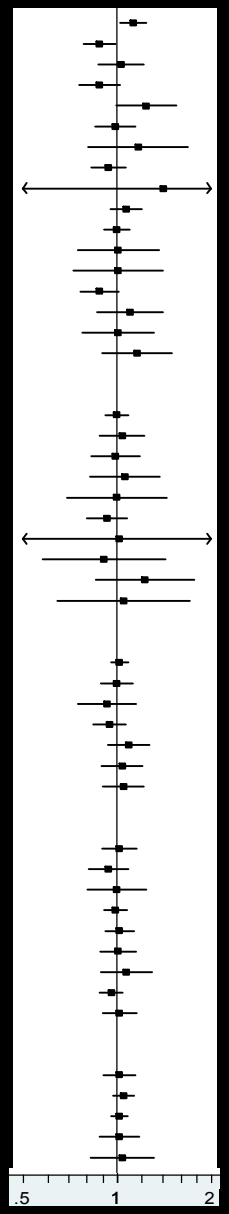
	LPL	N291S	21	38028
	LPL	S447X	26	31269
	LPL	D9N	21	28325
	LPL	PvuII	18	17214
	LPL	T-93G	7	15440
	LPL	HindIII	23	11470
	LPL	G188E	3	11119
	PON1	Q192R	38	27522
	PON1	L55M	20	12416
	PON1	T-107C	4	2698
	PON2	S311C	7	3598
	CETP	TaqIB	7	8795
	apoB	SpIns/Del	19	8611
	apoB	XBaI	19	5574
	apoB	EcoRI	14	3577
Inflammation				
	IL6	G-174C	8	20301
	LTA	909253	5	15128
	THBS4	A387P	8	12723
	THBS1	T3949G	5	11124
	THBS2	N700S	4	8207
	TNF-alpha	G-308A	17	12418
	TNF-alpha	G-238A	2	1858
	TLR4	D299G	7	10301
	MMP3	5A/6A	7	5751
	MMP9	C-1562T	5	5160
Vascular				
	ACE	I/D	40	41014
	AGT	M235T	41	29980
	AGT	T174M	16	20572
	eNOS	E298D	40	25495
	eNOS	T-786C	21	22833
	eNOS	Intron 4	30	19028
	AGT1R	A1166C	25	25147
Haemostasis				
	Factor V	R506Q	57	42030
	GPIIIa	P1A1/A2	44	34140
	Factor II	G20210A	32	25324
	PAI-1	4G/5G	35	23158
	Factor VII	R353Q	24	18092
	GPIa	C807T	15	11851
	GPIba	T-5C	13	10083
	FGB	G-455A	20	30935
	Factor XIII	V34L	16	12277
Others				
	HFE	C282Y	23	59944
	HFE	H63D	13	54368
	MTHFR	C677T	80	44558
	ESR1	T-397C	8	16706
	ADRB3	W64R	10	9024



Empirical study of bias

- Main reason for detailed collection study-level data
- Investigating whether factors such as study size, investigator blinding, study location etc. consistently affect the results of meta-analyses.
- Using ratio of odds ratios (ROR) approach
  - E.g. early results suggest that the ROR between the initial study and following studies is 1.12 (1.03-1.22) suggesting that initial studies have, on average, a 12% higher odds ratio.

Future plans

- Study effects of publication bias and reporting bias
- Publish CHD synopsis
- Obtain funding to turn synopsis/database into maintained online resource
- Expand database to include all association studies, regardless of inclusion in systematic reviews
- Develop infrastructure to deal with inclusion of GWA studies and integration with existing candidate gene studies

Collaborators

Julian Higgins & UK HuGENet Coordinating Centre

www.hugenet.org.uk

John Danesh & Molecular Epidemiology Unit, University of Cambridge

www.phpc.cam.uk/MEU

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www.nihr.ac.uk